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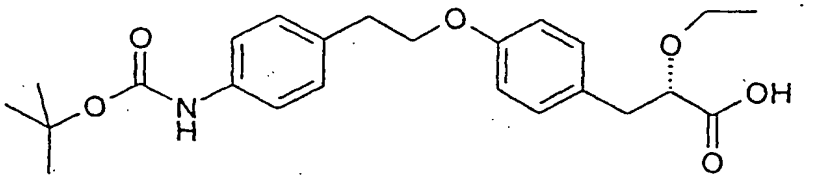
(54) Title: CRYSTALLINE FORM OF 3-{4-[2-(4-*TERT*-BUTOXYCARBONYLAMINOPHENYL)ETHOXY]PHENYL}-(S)-2-ETHOXY PROPANOIC ACID



(I)

(57) Abstract: The present invention relates to crystalline forms of the compound 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid as shown in formula (I), or a pharmaceutically acceptable salt thereof, and any solvates thereof. The invention also concerns methods of treating one or more metabolic diseases, particularly those associated with Insulin Resistance Syndrome, and the use of the crystalline form of the compound, or a pharmaceutically acceptable salt thereof, or a solvate thereof, in the manufacture of a medicament for therapeutic use in one or more metabolic diseases. The invention further concerns pharmaceutical compositions containing the crystalline form of the compound, or a pharmaceutically acceptable salt thereof, or a solvate thereof, as active ingredient, as well as processes for the manufacture of the crystalline form of the compound, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

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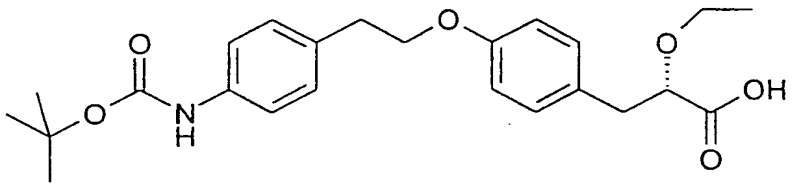
Crystalline Form

The present invention relates to crystalline forms of the compound 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, shown by the formula I (set out below),



I

or pharmaceutically acceptable salts thereof, and any solvates thereof. The invention also concerns methods of treating one or more metabolic diseases, particularly those associated with Insulin Resistance Syndrome, and the use of a crystalline form of the compound, or a pharmaceutically acceptable salt thereof, or a solvate thereof, in the manufacture of a medicament for therapeutic use in one or more metabolic diseases. The invention further concerns pharmaceutical compositions containing a crystalline form of the compound, or a pharmaceutically acceptable salt thereof, or a solvate thereof, as active ingredient, as well as processes for the manufacture of a crystalline form of the compound, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

In the formulation of drug compositions, it is important for the drug substance to be in a form in which it can be conveniently handled and processed. This is of importance in obtaining a commercially viable manufacturing process, and also for subsequent manufacture of pharmaceutical formulations comprising the active compound.

Chemical stability, solid state stability, and shelf life of the active ingredients are also very important factors. The drug substance, and compositions containing it, should be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the active component's physico-chemical characteristics (e.g. its chemical composition, density, hygroscopicity and solubility).

Moreover, it is also important to be able to provide drug in a form which is as chemically pure as possible.

Amorphous materials may present significant problems in this regard. For example, such materials are typically more difficult to handle and to formulate compared with crystalline forms, provide for unreliable solubility, and are often found to be unstable and chemically impure.

The skilled person will appreciate that, if a drug can be readily obtained in a stable crystalline form, the above problems may be solved.

Thus, in the manufacture of commercially viable and pharmaceutically acceptable, drug compositions, it is desirable, wherever possible, to provide drug in a substantially crystalline, and stable, form.

It is to be noted, however, that this goal is not always achievable. Indeed, typically, it is not possible to predict, from molecular structure alone, what the crystallisation behaviour of a compound will be, and this can usually only be determined empirically.

The above compound is intended for therapeutic use in Insulin Resistance Syndrome (IRS) which refers to a cluster of manifestations including insulin resistance with accompanying hyperinsulinaemia, possible type 2 diabetes mellitus, arterial hypertension, central (visceral) obesity, dyslipidaemia observed as deranged lipoprotein levels typically characterised by elevated VLDL (very low density lipoproteins) and reduced HDL (high density lipoproteins) concentrations and reduced fibrinolysis.

Recent epidemiological research has documented that individuals with insulin resistance run a greatly increased risk of cardiovascular morbidity and mortality, notably suffering from myocardial infarction and stroke. In type 2 diabetes mellitus these atherosclerosis related conditions cause up to 80% of all deaths.

In clinical medicine there is awareness of the need to increase the insulin sensitivity in IRS and thus to correct the dyslipidaemia which is considered to cause the accelerated progress of atherosclerosis. However, currently this is not a universally well-defined disease.

The present invention relates to a crystalline solid form of the compound of formula I. Significant advantages can arise when the compound of formula I can be isolated in a crystalline form, for example, in the manufacture of the compound to the purity levels and uniformity required for regulatory approval and for ease and uniformity of formulation. It is therefore highly desirable to find a novel crystalline form of the compound.

We present as a feature of the invention a crystalline form of a compound of formula I, or a solvate thereof. In an alternative feature of the invention we present a crystalline form of a pharmaceutically acceptable salt of the compound of formula I, or a solvate thereof.

We have isolated the compound of formula I as a crystalline solid that exists in a form which is substantially or essentially free of solvent (hereinafter referred to as the "anhydrous" form). Alternatively a solvated form may be formed, for example, a hydrated form. In a further alternative we have also isolated a crystalline form of the sodium salt of the compound of formula I.

By the use of the term "solvated" we include the term hydrated.

A crystalline form of the compound of formula I can be defined by reference to its melting point, powder X-ray diffraction pattern and single crystal X-ray data.

The melting point of the crystalline form of the compound of formula I generally depends on the level of purity and may be determined by conventional procedures well known in the art, for example, by differential scanning calorimetry (DSC). Typically, the crystalline form of the compound of formula I has a melting point which is in the range 102-112°C, for example about 105-109°C, when it is substantially or essentially in the anhydrous form.

The crystalline form of the compound of formula I, when it is substantially or essentially in the anhydrous form, has an X-ray powder diffraction pattern containing specific peaks of high intensity at 9.3, 5.5, 4.89, 4.83, 4.67, 4.22, 3.82 and 3.62 Å. Additional specific peaks of lower relative intensity to the first peaks are at 14.4, 6.0, 5.7, 4.99, 4.53, 4.46, 4.33, 4.28, 3.99, 3.70, 3.54, 3.47, 3.07 and 2.59 Å.

Crystalline compound of formula I may be obtained from a non-crystalline form of the compound of formula I, by crystallisation from a suitable solvent (including organic solvents, aqueous solutions and mixtures thereof), such as isooctane, butylacetate and toluene, or a mixture of solvents, such as a mixture of ethanol and water. To initiate crystallisation, seeding with crystalline compound of formula I may be required. Crystallisation of the compound from an appropriate solvent system may be achieved by attaining supersaturation, for example, by cooling, by solvent evaporation and/or by the addition of an anti-solvent (a solvent in which the compound of formula I is poorly soluble, examples of suitable anti-solvents include heptane and isooctane). Crystallisation temperatures and times will vary depending upon the concentration of the compound in solution, the solvent system used and the method of crystallisation adopted.

Crystalline forms of the compound of formula I may be isolated using techniques well known to those skilled in the art, for example, by decanting, filtration or centrifuging. Similarly the crystalline form may be dried in accordance with well-known procedures.

Optional re-crystallisation step(s) may be performed using the same or different solvent systems to reduce further impurities, such as amorphous material, chemical impurities or to convert the crystalline into a solvated/hydrated form or an anhydrous form.

Preferably the compound of formula I is crystallised directly from the reaction solution or may be crystallised from a subsequent solution.

A further feature of the invention is a process for the production of a crystalline form of a compound of formula I which comprises crystallising the compound of formula I.

By the use of the term "substantially or essentially in the anhydrous form", we do not exclude the presence of some solvent, including water, within the crystal lattice structure. Solvent, including water, may also be present outside the crystal lattice structure.

A feature of the invention is a crystalline form of a compound of formula I, as described above, for use in medical therapy.

According to a further feature of the invention there is provided a pharmaceutical composition which comprises a crystalline form of a compound of formula I, as described above, in association with a pharmaceutically acceptable diluent or carrier, or the use of a crystalline form of a compound of formula I as described above in association with a pharmaceutically acceptable diluent or carrier.

The composition may be in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use, for example a cream, ointment, gel or aqueous or oily solution or suspension; for nasal use, for example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example as a finely divided powder such as a dry powder, a microcrystalline form or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oily solution or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The amount of a crystalline form of a compound of formula I, as described above, that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.001 mg to 50 mg of active agent mixed with an appropriate and convenient amount of excipient(s) which may vary from about 10 to about 99.9999 percent by weight of the total composition. Dosage unit forms will generally contain about 0.001 mg to about 50 mg of an active ingredient.

The invention also includes the use of the crystalline compound of the invention, as described above in the production of a medicament for use in:

(i) treating dyslipidaemia;

(ii) treating type 2 diabetes mellitus;

(iii) treating hyperglycaemia;

(iv) treating hyperinsulinaemia;

(v) treating hyperlipidaemia;

(vii) treating arterial hypertension; and/or

(viii) treating abdominal obesity.

The invention also includes a method of producing an effect as defined hereinbefore or treating a disease or disorder as defined hereinbefore which comprises administering to a warm-blooded animal, preferably humans, requiring such treatment, an effective amount of a crystalline form of a compound of formula I, as described above.

The size of the dose for therapeutic or prophylactic purposes of a crystalline form of a compound of formula I will naturally vary according to the nature and severity of the medical condition, the age and sex of the animal or patient being treated and the route of administration, according to well known principles of medicine.

A crystalline form of the compound of formula I may be administered as a sole therapy or it may be administered in conjunction with other pharmacologically active agents such as an anti-diabetic, anti-hypertensive, diuretic or anti-hyperlipidaemic agent.

Crystalline forms prepared in accordance with the Example(s) below showed essentially the same powder X-ray diffraction patterns and/or DSC thermograms. It was clear when comparing the relevant patterns/thermograms (allowing for experimental error) that the same crystalline form had been formed. DSC onset temperatures may vary in the range ±5°C (for example ±2°C), and powder X-ray diffraction pattern distance values may vary in the range ±5 on the last decimal place.

Synthesis 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid

a) 4-(2-Hydroxyethyl)phenylcarbamic acid *tert*-butyl ester

2-(4-aminophenyl)ethanol (500 g, 3.65 mol) was charged to THF (4000 ml). The mixture was cooled to 0 °C. Di-*tert*-butyl dicarbonate (796 g, 3.65 mol), was dissolved in THF (1000 ml). The THF solution of di-*tert*-butyl dicarbonate was then charged to the 2-(4-aminophenyl)ethanol in THF at 0 °C over 100 minutes. The mixture was heated to 20 °C over 3 hours and then stirred for 13 hours at 20 °C. Additional di-*tert*-butyl dicarbonate (41 g, 0.05 eq) was then charged portion-wise over 4 hours to take the reaction to completion . The THF was then evaporated. The residue (1450 g) was poured out on heptane under stirring. The slurry formed was filtered and the crystals washed with heptane (1000 ml). The crystals were dried under reduced pressure at 35 °C yielding 822 grams of 4-(2-hydroxyethyl)phenylcarbamic acid *tert*-butyl ester.

b) 2-[4-*tert*-Butoxycarbonylaminophenyl]ethyl-(4-methylphenyl) sulfonate

4-(2-Hydroxyethyl)phenylcarbamic acid *tert*-butyl ester (822 g, 3.46 mol) was dissolved in methylene chloride (4800 ml). Pyridine (548 g, 6.93 mol) was added and the solution cooled to 13 °C. p-Toluenesulphonyl chloride (991 g, 5.2 mol) was dissolved in methylene chloride (2400 ml). The solution containing p-toluenesulphonyl chloride was charged over one hour to the solution of 4-(2-hydroxyethyl)phenylcarbamic acid *tert*-butyl ester. The reaction was heated to 20 °C over 2.5 hours. The reaction was then kept at 20-25 °C for 18 hours. The methylene chloride solution was then washed with water (2×4000 ml) and afterwards dried with $MgSO_4$ (130 g). The salt was filtered off and the solvent evaporated. The remaining (2000 g) was poured out on heptane (5000 ml). The crystals formed were filtered off and washed with heptane (2000 ml), yielding 1600 g (wet) (drying sample gave 1320 g). The wet substance was then re-crystallised.

2-[4-*tert*-Butoxycarbonylaminophenyl]ethyl-(4-methylphenyl) sulfonate (wet, 3209 g) was dissolved in ethanol (6000 ml) at 55 °C. Water (600 ml) was charged and the solution was cooled to 48 °C where crystallisation took place. The slurry was kept at 48 °C for 30 minutes and then cooled to 3 °C over 3 hours. The crystals were filtered and washed with cold ethanol (2×500 ml). The crystals were dried under reduced pressure at 35 °C for 25 hours, yielding 2330 g of 2-[4-*tert*-butoxycarbonylaminophenyl]ethyl-(4-methylphenyl) sulfonate.

c) 3-{4-[2-(4-*tert*-Butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxypropanoic acid ethyl ester

(S)-2-Ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester (250 g, 1.05 mol, 1.0 eq) was dissolved in dimethylsulphoxide (DMSO) (500 ml). When a homogenous solution was formed, NaOH (s) beads, 20-40 mesh (48.2 g, 1.21 mol, 1.15 eq) was added followed by addition of a further 500 ml DMSO. 2-[4-*tert*-butoxycarbonylaminophenyl]ethyl-(4-methylphenyl) sulfonate (431 g, 1.10 mol, 1.05 eq) was dissolved in DMSO (1000 ml). The DMSO solution of 2-[4-*tert*-butoxycarbonylaminophenyl]ethyl-(4-methylphenyl) sulfonate was then added over 10 minutes at 20-25 °C to the solution of (S)-2-Ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester. The reaction mixture was then stirred for 1 hour. To fully convert (S)-2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester to 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxypropanoic acid ethyl ester an additional amount 2-[4-*tert*-butoxycarbonylaminophenyl]ethyl-(4-methylphenyl) sulfonate (20g, 0.05 mol, 0.05 eq) and NaOH (s) beads, 20-40 mesh (2.1 g, 0.05 mol, 0.05 eq) was added. The reaction mixture was stirred for another 3 hours. The mantle was then cooled to 10°C.

d) 3-{4-[2-(4-*tert*-Butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid

NaOH (aq) 1M (1.15 l, 1.15 mol, 1.10 eq) was added to a solution of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxypropanoic acid ethyl ester over 30

The water layer was washed with methyl *tert*-butylether (3×2000 ml). The water layer was then acidified to pH 3 with $KHSO_4$ (aq) 1M (1.6 l, 1.6 mol, 1.5 eq). The acidic water solution was then extracted with ethyl acetate (3×2000 ml). The ethyl acetate parts were put together and washed with H_2O (4×2000 ml). The ethyl acetate solution was dried with $MgSO_4$ (90 g). The salts were filtered off and washed with ethyl acetate (3×100 ml). The filtrate was evaporated to dryness. The oil residue (750 g) was dissolved in toluene (1750 ml). The solution was seeded with crystals of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid and the crystallisation was continued for 30 minutes. Then isooctane (3500 ml) was added. The slurry was stirred for 15 minutes and then filtered. The solid was washed with toluene:isooctane 1:2 (400 ml) followed by water (300 ml). Drying at 40°C at reduced pressure yielded 382 g (0.89 mol) of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid as a white powder.

Re-crystallisation from Butyl acetate and Isooctane

3-{4-[2-(4-*tert*-Butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid (382 g, 0.89 mol, 1.0 eq) was dissolved in butyl acetate (2100 ml) at 40°C. The solution was cooled to -5°C and then seeded with crystals of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid. The crystallisation started immediately. The mixture was cooled to –15°C over 1 hour. Isooctane (2000 ml) was then added to the slurry over 50 minutes. The slurry was stirred for another 10 minutes and then filtered off. The solid was then washed with cold butyl acetate:isooctane 1:1 (1000 ml). The solid was dried using reduced pressure at 40°C, yielding 340 grams (0.79 mol) of crystals of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid as a white powder.

Re-crystallisation from Ethanol and H_2O

Two batches of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid (680 g, 1.58 mol, 1.0 eq) were dissolved in ethanol (2100 ml) at 40°C. To the solution H_2O (1000 ml) was added over 20 minutes at 40°C. The solution was seeded with crystals of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic

acid (0.3 g). H_2O (4100 ml) was added over 70 minutes. The slurry was then cooled to 5°C over 100 minutes. The slurry was stirred for another 20 minutes and then filtered off. The solid was washed with cold ethanol:H_2O 2:5 (1500 ml). The solid was dried using reduced pressure at 55°C, yielding 667 grams (1.55 mol) 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid as a white solid.

Melting Point Determination

Differential scanning calorimetry (DSC) was performed using a Mettler DSC820 instrument, according to standard methods, for example those described in: Höhne, G. W. *et al* (1996), *Differential Scanning Calorimetry*, Springer, Berlin.

DSC of the anhydrous form showed an endotherm with an extrapolated onset temperature of *ca* 107 °C (*ca* 112 J/g). Thermogravimetric analysis was performed using a Mettler Toledo TGA850 instrument and showed a decrease in mass of *ca* 0.15% when the compound melts, followed by decomposition.

DSC of the anhydrous form of the sodium salt showed an endotherm with an extrapolated onset temperature of *ca* 173°C (*ca* 54 J/g). Thermogravimetric analysis was performed using a Mettler Toledo TGA850 instrument and showed a decrease in mass of *ca* 1% when the compound melts, followed by decomposition

X-ray Powder Diffraction Pattern Determination

X-ray powder diffraction analysis (XRPD) was performed on samples prepared according to standard methods, for example those described in: Giacovazzo, C. *et al* (1995), *Fundamentals of Crystallography*, Oxford University Press; Jenkins, R. and Snyder, R. L. (1996), *Introduction to X-Ray Powder Diffractometry*, John Wiley and Sons, New York; Bunn, C. W. (1948), *Chemical Crystallography*, Clarendon Press, London; or Klug, H. P. and Alexander, L. E. (1974), *X-Ray Diffraction Procedures*, John Wiley and Sons, New York. X-ray analyses were performed using a Siemens D5000 diffractometer and/or a Philips X'Pert MPD diffractometer.

The crystals of an anhydrous form were analysed by XRPD and the result is tabulated below in Table 1 (in which RI represents relative intensity), and shown in Figure 1. The diffractogram was measured with variable slits and without internal standard. The intensities are based on the intensities observed in a variable slit measurement without background subtraction. The relative intensities are less reliable, and instead of numerical values, the following definitions are used:

% Relative Intensity	Definition
25-100	vs (very strong)
10-25	s (strong)
3-10	m (medium)
1-3 %	w (weak)

Some additional weak or very weak peaks found in the diffractogram have been omitted from Table 1.

Table 1. X-ray powder diffraction data for the anhydrous crystalline form of the compound of formula I, shown in Figure 1.

d-value/Å	RI	d-value/Å	RI
14.4	s	3.42	m
9.7	m	3.36	m
9.3	vs	3.31	m
8.6	m	3.11	m
7.2	m	3.07	s
7.1	m	3.03	m
6.0	s	3.00	m
5.7	s	2.95	m
5.5	vs	2.90	m
5.2	m	2.84	m

4.99	s	2.79	m
4.89	vs	2.77	m
4.83	vs	2.59	s
4.67	vs	2.46	m
4.53	s	2.43	m
4.46	s	2.34	m
4.33	s	2.31	m
4.28	s	2.28	m
4.22	vs	2.24	m
4.05	m	2.20	m
3.99	s	2.17	m
3.90	m	2.11	m
3.82	vs	2.08	m
3.70	s	2.00	m
3.62	vs	1.96	m
3.54	s	1.91	m
3.47	s		

It will be understood that the d-values of the X-ray powder diffraction patterns may vary slightly from one instrument to another and so the values quoted are not to be construed as absolute. It is reasonable to assume that a crystalline form of a compound of formula I is that which is described herein if the d-values are within ± 5 on the last decimal place, especially if within ± 2 on the last decimal place.

Single Crystal Structure Determination

The unit cell and the crystal structure of the anhydrous form were determined from single crystal X-ray data. The unit cell was orthorhombic, with the space group $P2_12_12_1$, $Z = 4$ and the dimensions $a = 5.341$, $b = 18.757$, $c = 23.062$ Å, $\alpha = \beta = \gamma = 90°$ and $V = 2310.4$ Å^3.

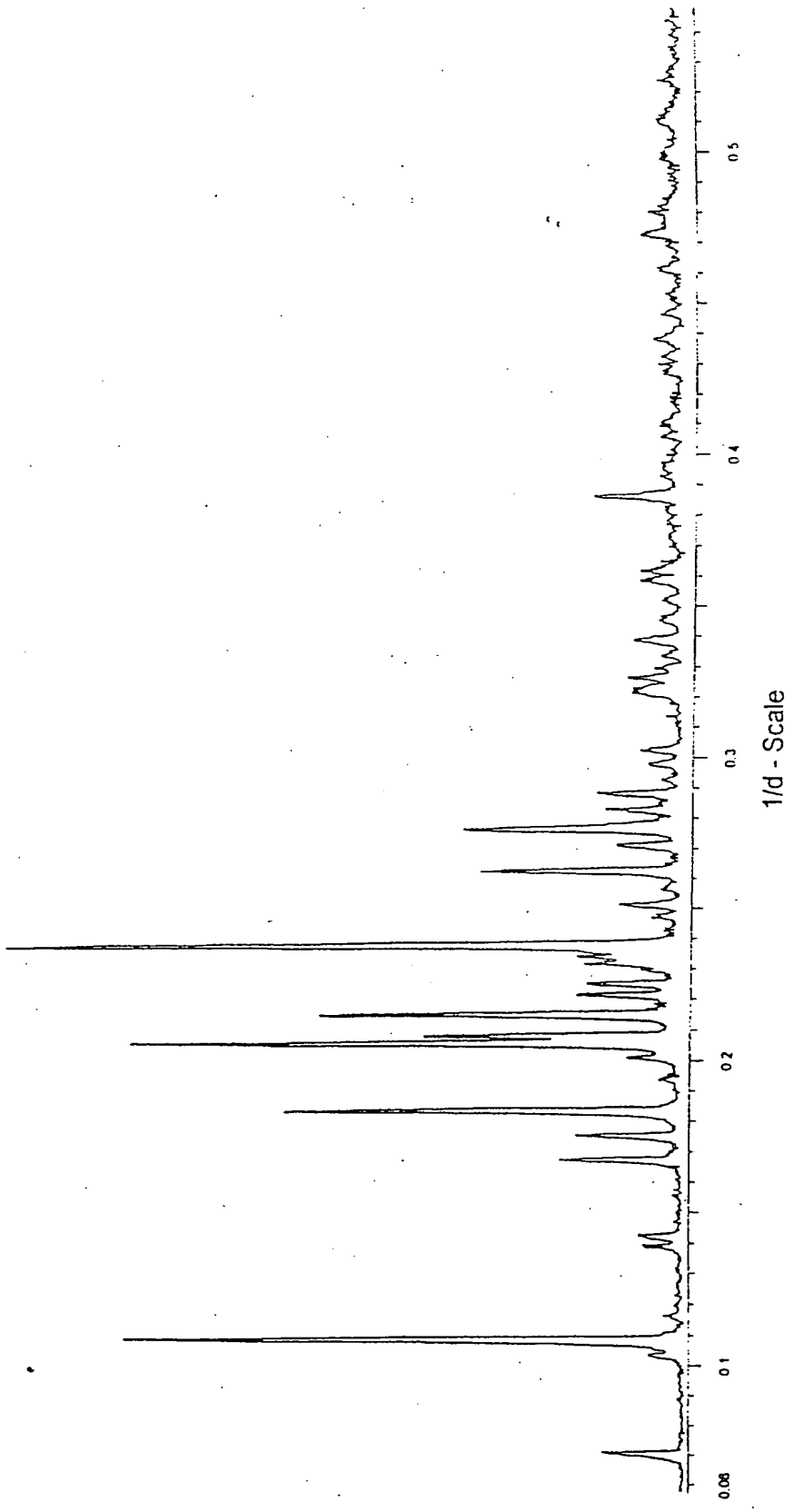
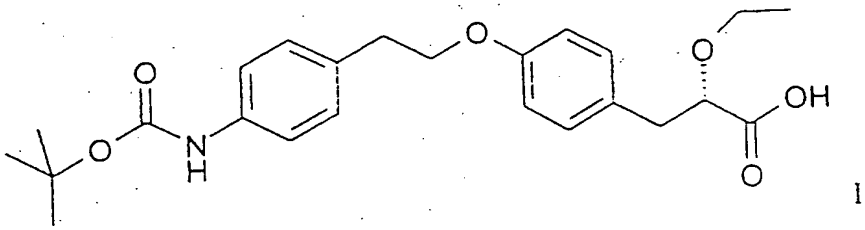


Fig. 1.

Claims

1. A crystalline form of the compound 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, shown in formula I below,



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or a pharmaceutically acceptable salt thereof or a solvate thereof.

2. A crystalline form as claimed in claim 1, which is substantially or essentially free of solvent.

3. A crystalline form as claimed in claim 2 characterised in that it has a melting point of between 102 and 112°C.

4. A crystalline form as claimed in claim 2 characterised in that it has a X-ray powder diffraction pattern containing specific peaks of high intensity at 9.3, 5.5, 4.89, 4.83, 4.67, 4.22, 3.82 and 3.62 Å.

5. A crystalline form as claimed in claim 4 characterised in that it has a X-ray powder diffraction pattern having additional specific peaks of lower relative intensity to the first peaks at 14.4, 6.0, 5.7, 4.99, 4.53, 4.46, 4.33, 4.28, 3.99, 3.70, 3.54, 3.47, 3.07 and 2.59 Å.

6. A crystalline form of a sodium salt of the compound shown in formula I above, characterised in that it has a DSC thermogram showing an endotherm with an extrapolated onset temperature between 168-178 °C.

7. A crystalline form of a compound of formula I, as claimed in any claim from 1 to 5, for use as a medicament.

8. A pharmaceutical formulation comprising a crystalline form of a compound of formula I, as defined in any claim from 1 to 5, and a pharmaceutically acceptable adjuvant, diluent or carrier.

9. Use of a crystalline form of a compound of formula I, as defined in any claim from 1 to 5, in the preparation of a medicament for the treatment or prophylaxis of metabolic disease conditions, including insulin resistance syndrome.

10. The use of a substance as defined in any claim from 1 to 5 in the production of a medicament for use in treating metabolic disorders.

11. A method for treatment or prophylaxis of conditions associated with reduced sensitivity to insulin, which method comprises administering a therapeutically effective amount of a compound according to any one of claims 1 to 5 to a patient having such reduced sensitivity to insulin.

12. A method for treatment or prophylaxis of dyslipidaemia, type 2 diabetes mellitus, hyperglycaemia, hyperinsulinaemia, arterial hypertension and/or abdominal obesity, which method comprises administering a therapeutically effective amount of a compound according to any one of claims 1 to 5 to a patient in need of such treatment or prophylaxis.

13. A process for the preparation of a crystalline form of a compound of formula I which comprises crystallising a compound of formula I.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02379

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 271/28, A61K 31/325, A61P 5/48, A61P 3/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9962870 A1 (ASTRA AKTIEBOLAG), 9 December 1999 (09.12.99), page 4; page 20, line 25 - page 21, line 15, the claims	1,2,7-13
P,A	--	3-6
P,A	WO 9962871 A1 (ASTRA AKTIEBOLAG), 9 December 1999 (09.12.99), claims 1, 32, 33	1-13
	--	

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 March 2001	16 -03- 2001

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02379

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11, 12
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest

Claims 11, 12 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions

INTERNATIONAL SEARCH REPORT

Information on patent family members

25/02/01

International application No.
PCT/SE 00/02379

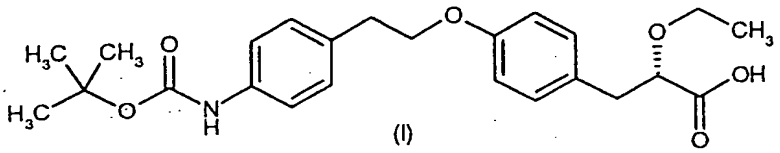
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9962870 A1	09/12/99	AU 1182299 A	31/05/99
		AU 4667099 A	20/12/99
		AU 4667299 A	20/12/99
		BR 9813192 A	29/08/00
		EP 1029424 A	23/08/00
		NO 20006114 D	00/00/00
		NO 20006116 D	00/00/00
		SE 9801990 D	00/00/00
		WO 9962871 A	09/12/99
WO 9962871 A1	09/12/99	AU 1182299 A	31/05/99
		AU 4667099 A	20/12/99
		AU 4667299 A	20/12/99
		BR 9813192 A	29/08/00
		EP 1029424 A	23/08/00
		NO 20006114 D	00/00/00
		NO 20006116 D	00/00/00
		SE 9801990 D	00/00/00
		WO 9962870 A	09/12/99
		AU 1058399 A	24/05/99
		EP 1027769 A	16/08/00
		SE 9801991 D	00/00/00
		AU 1182399 A	31/05/99
		AU 4667199 A	20/12/99
		NO 20006115 D	00/00/00
		SE 9801992 D	00/00/00
		WO 9962872 A	09/12/99

WO200140165-A1

AstraZeneca AB

Crystalline 3-{4-[2-(4-tert-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid - useful for the treatment of e.g. metabolic disorders, insulin resistance syndrome, dyslipidaemia, hyperglycaemia and arterial hypertension.

Drug Activity: Crystalline; Antidiabetic; Antilipemic; Hypotensive; Anorectic
Mechanism of Action: Hypoglycemic
Compound Name: None Given



(I)

Use: For the treatment of metabolic disorders, insulin resistance syndrome, reduced sensitivity to insulin, dyslipidaemia, type 2 diabetes mellitus, hyperglycaemia, hyperinsulinaemia, arterial hypertension and abdominal obesity (claimed).
Dosage: 0.001 - 50 mg orally. Administration is also topical, vaginal, rectal, parenteral, sublingual, buccal, intravenous, subcutaneous, intramuscular or by inhalation or infusion.
Advantage: None given.
Biological Data: No suitable data given.
Chemistry: A crystalline 3-{4-[2-(4-tert-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid (I) or a salt or solvate of (I) are claimed.

20 pages

Drawings 0/0

Authors: Boije M; Bohlin M
Location: Soderjalie, Sweden
Publication Date: 07 June 2001
Language: English
Priority: 17 April 2000 SE-001422
Document Number: WO200140165-A1
Filed: 29 November 2000 as SE2379
Designated States: Regional: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE (ARIPO) (Eurasian) (OAPI) National: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW